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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/074,178	02/12/2002	David J. Eyre	7475-69889	5007

49437 7590 03/21/2007
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INDIANAPOLIS, IN 46204

EXAMINER

SMITH, CAROLYN L

ART UNIT	PAPER NUMBER
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1631

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/074,178

Applicant(s)

EYRE

Examiner

Carolyn L. Smith

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 December 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 18-24 and 26 is/are pending in the application.
- 4a) Of the above claim(s) 24 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 18-23 and 26 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date: _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Applicant's amendments and remarks, filed 12/28/06, are acknowledged. Amended claims 18, 20, and 21 and new claim 26 are acknowledged. Claim 24 remains withdrawn due to being drawn to a non-elected specie.

Applicant's arguments, filed 12/28/06, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from the previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claims 18-23 and 26 are herein under examination.

Claim Rejections - 35 USC § 112, First paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

NEW MATTER

Claims 18-23 and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant points to written support for claim amendments on pages 11, 13, 14, and 20. There does not appear to be adequate written support for the amended limitation “by evaluating a function that depends on the first score and the second score as independent variables of the function” (instant claim 18). The pages specified by Applicant do not mention “evaluating a function that depends on the first score and the second score as independent variables of the function”. Looking elsewhere in the specification, while page 9, third paragraph, states “to provide algorithms capable of being independent of the fluorescence intensity”, this does not provide written support for independent variables of a function which differs in scope. While the specification mentions a baseline is determined by choosing a cycle in a well-behaved shape curve whose first derivative is closest to zero prior to the cycle with the maximum second derivative (page 12, last paragraph), this passage is narrower in scope than the amended limitation.

Because the introduction of “by evaluating a function that depends on the first score and the second score as independent variables of the function” (instant claim 18) does not have adequate written support in the specification, claims, and/or drawings of the original disclosure, this limitation is considered to be NEW MATTER. Claims 19-23 and 26 are also rejected due to their dependency from claim 18.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

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pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

LACK OF ENABLEMENT

Claims 18-23 and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 18 recites a device for determining the *presence* of a nucleic acid in a sample comprising an instrument for temperature cycling, a fluorimeter, and a processor that determines whether a sample is *indeterminate* for the presence of the nucleic acid. One skilled in the art would not exactly know what to do with a device that determines indeterminacy. The specification on page 20, last paragraph, mentions the number of correct calls in the unable-to-call or "indeterminate" category as well as a function that is designed to decrease the number of

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correct calls in the unable-to-call region. If the function is designed to decrease the number of correct calls in the unable-to-call region, one skilled in the art would still need to undergo undue experimentation to determine what is actually determinate so that sound scientific conclusions could be made on the sample. Due to the undue experimentation on finding out exactly what one would exactly do with this device, this invention lacks enablement. Claims 19-23 and 26 are also rejected due to their dependency from claim 18.

Claim Rejections - 35 USC § 112, Second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18-23 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The preamble of claim 18 recites determining the presence of a nucleic acid in a sample whereas the body of the claim recites determining whether the sample is indeterminate for the presence of the nucleic acid. Therefore, it is unclear if the preamble or the body of claim 18 is controlling the metes and bounds of this claim. Clarification of this issue via clearer claim wording is requested. Claims 19-23 and 26 are also rejected due to their dependency from claim 18.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 18-23 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wittwer (US 6,387,621 B1) in view of Schork et al. (US 6,291,182 B1) and Clark et al. (US 6,656,428 B1).

Wittwer describes a system with a rapid thermal cycling device using capillary tubes and hot air temperature control (col. 4, line 66 to col. 5, line 2) which represents the instrument in instant claim 18, 22, and 23. Wittwer describes analyzing a sample for the presence of a nucleic acid using polymerase chain reaction and a fluorescent detecting entity (col. 1, lines 13-18) as stated in the preamble of instant claim 18. Wittwer describes amplification with product analysis for “real-time” PCR in the same instrument (col. 1, lines 25-40). Wittwer describes the LightCycleTM as a rapid temperature cycler with a fluorimeter (col. 5, lines 42-44) which is a PC-based instrument with integrated algorithms in the LightCycleTM platform (col. 5, lines 45-57) which represents a temperature cycler, fluorimeter, and processor, as stated in instant claim 18. Wittwer describes determining the presence of a nucleic acid by analyzing fluorescent entity measurements capable of detecting the nucleic acid and its number during amplification via slope analysis of fluorescence intensity (col. 2, lines 27-52) and a fluorescent entity providing a signal related to the quantity of the nucleic acid (claim 1), as stated in instant claim 18. Wittwer describes comparing fluorescent values after each amplification cycle (col. 2, lines 45-52) and

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detection via a fluorimeter (col. 5, lines 42-44). Wittwer describes the automated process involving a thermal cycler having a sensor for reporting fluorescence values as a function of cycle number and a processor programmed with an algorithm to process values and report a positive or negative result (col. 2, lines 53-58). Wittwer describes inputting data (col. 7, line 59) and initiation of the analysis algorithm prior to the completion of temperature cycling (col. 2, first paragraph), as stated in instant claim 18. Wittwer describes the maximum slope (first derivative) is obtained from the sliding window analysis and the second derivatives are calculated by a 3-point sliding window linear regression of the first derivatives which provide arrays $Y'i$ and $Y''i$ (col. 7, lines 20-24 and col. 8, lines 12-25) which represents initiating first and second algorithms to obtain first and second scores, as stated in instant claim 18. Wittwer describes first derivative estimate, second derivative estimate, and confidence band factor as well as using an algorithm where the fluorescent values determine the first and second derivatives (i.e. first and second scores) which correspond to cycle numbers and assigning derivative values to the certain cycle numbers after which a baseline, baseline region and confidence intervals for a predicted negative test point are determined (i.e. Figure 7; col. 7, line 46 to col. 8, line 67; col. 3, lines 22-30), a composite score denoted by a rightmost large black circle as well as the baseline on Figures 7-11, wherein the baseline is determined from a well-behaved shape curve whose first derivative is closest to zero chosen from among all cycles prior to the cycle with the maximum second derivative (col. 8, lines 26-44), and using a test point cycle to determine against the baseline for determining a positive or negative result (col. 8, lines 45-52) which represents obtaining first, second, and composite scores via evaluating a function depending on the first and second scores to determine whether the sample is positive or negative, as stated in instant claims

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18 and 26. Wittwer describes using a confidence interval test (col. 8, lines 53-67). Wittwer describes accounting for background fluorescence and comparing fluorescent values to a baseline fluorescent region (col. 2, lines 45-47). Wittwer describes sample temperature tests using capillaries with forced air heating allowing precise control of temperature as well as using a rapid temperature cycler with a fluorimeter (col. 5, lines 8-44). Wittwer describes analysis occurring concurrently with amplification to decrease sample handling, save time, and reduce contamination risks (col. 1, lines 29-38). Wittwer describes reporting values as a function of cycle number and reporting results (col. 2, lines 53-58) and analyzing fluorescent measurements over a wide range of amplification cycles (col. 6, lines 48-63). Wittwer describes a maximum to baseline comparison (col. 6, first paragraph). Wittwer describes determining the test point cycle for determining a positive or negative result which may be the last cycle for a curve not well behaved (col. 8, lines 45-48). Wittwer does not teach all of the plurality of tests (as stated in instant claims 19-21) or determining if the sample is indeterminate for the presence of a nucleic acid (as stated in instant claim 18).

Schork et al. describe methods, software, and apparatus for determining the presence of a gene with a detectable trait in a genomic region (presence of a nucleic acid in a sample) (abstract). Schork et al. describe using a Perkin Elmer 9600 Thermocycler to perform amplification of nucleic acids (col. 47, lines 1-6). Schork et al. describe performing 40 cycles with 30 seconds at 95 degrees Celsius, 1 minute at 54 degrees Celsius and 30 seconds at 72 degrees Celsius (col. 47, lines 2-6) which represent rapid thermal cycling, as stated in instant claim 22. Schork et al. describe using a fluorimeter and Picogreen (fluorescence) to determine quantities of amplification products (col. 47, lines 7-9). Schork et al. describe excluding artifacts

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due to background noise by comparing two DNA strands (col. 47, lines 29-34) which represents a signal-to-noise ratio test, as stated in instant claim 19. Schork et al. describe using a variety of mathematic analysis tests, including Expectation-Maximization method (Maximum to Baseline Comparison Test) (col. 2, line 6), Wilcoxon rank test (function ordering test) (col. 2, line 62), Kolmogorov-Smirnov test (efficiency test using normal distribution) (col. 2, line 65), chi-square test (confidence interval test) (col. 2, line 50), and nonparametric tests (Last Rise Test) (Fig. 24), as stated in instant claims 19, 20, and 21. Schork et al. describe performing linkage analysis based upon establishing a correlation between transmission of genetic markers and that of a specific trait throughout generations within a family and statistical methods for determination of the likelihood that the marker and trait are segregating independently (col. 18, lines 39-64) which represents a type of Channel Consistency Test where the channel consistency is represented by the consistent flow (presence) or lack thereof of the marker and trait transmission throughout generations, as stated in instant claim 20. Schork et al. do not describe determining whether a sample is indeterminate for the presence of the nucleic acid.

Clark et al. describe determining the presence or amount of an analyte, such as a nucleic acid, in a sample via using a fluorimeter and an analytic instrument with a signal processor (abstract; claim 19; col. 6, second paragraph; col. 8, third paragraph). Clark et al. describe using an algorithm that allows the user the option of using certain symbology on a report to represent an indeterminate result (col. 31, last paragraph to col. 32, first paragraph and Figure 26a).

Wittwer, Schork et al., and Clark et al. provide methods and devices for determining the presence of a nucleic acid in a sample (abstract of each). Wittwer states there is a need for algorithms for detection, quantification, and genotyping (col. 2, lines 5-6). It would have been

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obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Wittwer by analyzing data with detection analysis tests as taught by Schork et al. wherein the motivation would have been to process data occurring during amplification including concomitant analysis results to modify temperature cycling as well as to acquire additional data during the latter stages of the amplification procedure to optimize amplification protocol and data quality, as stated by Wittwer (col. 2, lines 8-13). It would have been further obvious to modify the methods of Witter and Schork et al. by reporting an indeterminate result as taught by Clark et al. where the motivation would have been to provide cost effective analytical instruments that provide automated test results for single or low to medium sample volume applications and quality control of the test result, as stated by Clark et al. (col. 4, last paragraph and col. 10, last paragraph) as well as to acquire additional data during the latter stages of the amplification procedure to optimize amplification protocol and data quality, as stated by Wittwer (col. 2, lines 8-13).

Thus, Wittwer, in view of Schork et al. and Clark et al., make obvious the instant invention.

Applicant states he has amended instant claim 18 to recite the limitation "to determine whether the sample is indeterminate for the presence of the nucleic acid". This is acknowledged. Additional prior art has been added which makes this limitation obvious.

Conclusion

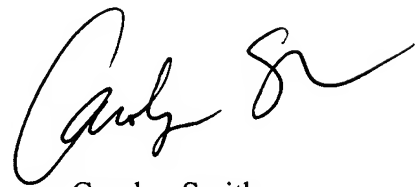
No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR §1.6(d)). The Central Fax Center number for official correspondence is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carolyn Smith, whose telephone number is (571) 272-0721. The examiner can normally be reached Monday through Thursday from 8 A.M. to 6:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, can be reached on (571) 272-0781.

March 15, 2007



Carolyn Smith
Examiner
AU 1631